

## REMARKS

Reconsideration of this application is requested. Claims 61 – 84 are active in the application subsequent to entry of this amendment. The claims have been amended to more particularly point out and distinctly claim that which applicants regard as their invention and to respond to the various objections and rejections set out in the current Action. For convenience a new set of claims is provided. The relationship between the previous claims and new claim set is discussed in the detailed remarks that follow and is as set out in the following table:

New claim	Previous claim(s)
61	33 + 35 + 38
62	36
63	37
64	39
65	40
66	41 (no changes)
67	42
68	43 (no changes)
69	44
70	45 (no changes)
71	46 (no changes)
72	47 (no changes)
73	48
74	49 (no changes)
75	50 + 51
76-84	52-60

Response is now provided to the various points/paragraphs in the Action in the order presented.

1. The examiner states that the Markush group represented by the term A has variably different definitions and renders the claims clearly improper. Claim 33 (now claim 61) is amended to specify As A<sup>2</sup>N-. Since the definition of A<sup>2</sup> is quite clear, the rejection is overcome.

The Action refers to "many pages of the specification" referring to "incorporation by reference" yet counsel notes only page 3 which is deleted from the specification. If there are other occurrences counsel would be pleased to know of them. In any event, the documents referred to are primarily mentioned for background information, do not represent "essential material" and are likely to be known by persons skilled in this art.

3. A substitute specification was indeed filed with the Amendment of January 4, 2002 according to my records- apparently it became detached during after filing processing. In any event attached is a substitute specification. This substitute specification is submitted under the provisions of 37 C.F.R. § 1.125(e). The substitute specification includes no new matter and a marked up version of the specification showing all changes is attached, thus the requirements of the rule have been satisfied. The attachment provides clear copies of the pages objected to and deletes the "incorporation" passage on page 3, as noted above.

5. The above amendment significantly restricts the scope of Claim 33 (now claim 61). Applicants submit that one skilled in the art could reasonably extrapolate the activities of representatives of the claimed compounds to the other compounds embraced by the claims which have not been tested. Tested compounds are mentioned in page 37, lines 11-15 and these data demonstrate compounds of the type encompassed by the claims are expected to have a high GH releasing activity.

6a. The definition of the term B in Claim 33 (now claim 61) is amended to read --- B is alkyl, cycloalkyl, aryl, arylalkyl, hydroxyarylalkyl, aryloxyarylalkyl or arylalkoxyalkyl ---. The amendment of the attachment also restricts the term A<sup>1</sup> to A<sup>2</sup>N-. The rejection is overcome.

6b. Indolylalkyl and quinolylalkyl are mentioned as examples of B in Claim 39 (now claim 64). These groups are encompassed by the term "arylalkyl" in Claim 33 (now claim 61)

7a. The amended claims do not include the phrase "lipophilic group". The rejection is overcome.

7b. The definition of D in Claim 33 (now claim 61) is amended to recite the specific structure appearing in original Claim 8. Claim 8 was not rejected in Paragraph 7b of the first action and accordingly the rejection is overcome.

7c. The definition of M<sup>1</sup> is amended to read --- M<sup>1</sup> is alkylene which may be substituted by halogen, hydroxy, (C<sub>1</sub>-C<sub>5</sub>)alkyl, and / or (C<sub>1</sub>-C<sub>5</sub>)alkoxy ---. See amended Claim 61. Intended substituents are clearly recited.

7d. The definition of A<sup>2</sup> is amended to --- A<sup>2</sup> is a single or fused ring, each ring constituting A<sup>2</sup> is an aliphatic or aromatic ring which may have at least one hetero atom, each ring constituting A<sup>2</sup> may be substituted by at least one group selected from halogen, hydroxy, alkyl, cycloalkyl, alkoxy, perfluoroalkyl, perfluoroalkoxy, cyano, nitro, mercapto, acyl, amino, acylamino and aryl ---. See amended Claim 33 (now claim 61) The definition of A<sup>2</sup> is clear.

7h. The definition of A<sup>3</sup>, A<sup>4</sup> and Z in Claim 36 (now claim 62) is amended to recite intended substituents.

7q. Claim 38, which corresponds to cancelled Claim 6, is cancelled. Claim 39 (now claim 64) corresponding to cancelled Claim 7 is amended to delete “substituted”.

7af. Claim 40 (now claim 65) corresponding to cancelled Claim 9 is amended to delete “substituted”.

7u. Claim 8 was cancelled in the response to the first action. Claim 33 (now claim 61) is clear in definition of the terms.

7s. Claim 38 is cancelled. Claim 39 depends on Claim 33 (now claim 61) and both indolylalkyl and quinolylalkyl are encompassed by the term “arylalkyl” in Claim 33 (now claim 61).

7v and w. the definition of R<sup>2</sup> and R<sup>3</sup> in Claim 33 (now claim 61) is amended to read --- R<sup>2</sup> and R<sup>3</sup> can be taken together with the nitrogen atom to which R<sup>2</sup> and R<sup>3</sup> are bonded to form a heterocycle ---. The definition of R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>1</sup> and R<sup>2</sup> is amended to read --- R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> .... can be taken together with R<sup>1</sup> or R<sup>2</sup> and the bridging group which links R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> or R<sup>8</sup> to R<sup>1</sup> or R<sup>2</sup> to form a carbocycle or heterocycle ---. The amended definitions are fully responsive and resolve the examiner's points.

7aa. The definition of R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> in Claim 33 (now claim 61) is amended to read --- R<sup>5</sup> and R<sup>7</sup>, or R<sup>6</sup> and R<sup>8</sup> can be taken together with the carbon atoms to which R<sup>5</sup> and R<sup>7</sup>, or R<sup>6</sup> and R<sup>8</sup> are bonded to form a carbocycle or heterocycle ---. The amended definition resolves the examiner's concerns.

7aj,. The phrase “said growth hormone” in Claims 44 (now claim 69) and 48 (now claim 73) are amended to read --- a growth hormone ---thus the rejection is overcome.

12. The definition of R<sup>2</sup> and R<sup>3</sup> in Claim 33 (now claim 61) is amended to read --- R<sup>2</sup> and R<sup>3</sup> can be taken together with the nitrogen atom to which R<sup>2</sup> and R<sup>3</sup> are bonded to form a heterocycle ---. The definition of R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>1</sup> and R<sup>2</sup> is amended to read --- R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> can be taken together with R<sup>1</sup> or R<sup>2</sup> and the bridging group which links R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> or R<sup>8</sup> to R<sup>1</sup> or R<sup>2</sup> to form a carbocycle or heterocycle ---. The definition of R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> in Claim 33 is amended to read --- R<sup>5</sup> and R<sup>7</sup>, or R<sup>6</sup> and R<sup>8</sup> can be taken together with the carbon atoms to which R<sup>5</sup> and R<sup>7</sup>, or R<sup>6</sup> and R<sup>8</sup> are bonded to form a carbocycle or heterocycle ---. No new matter is introduced into Claim 33 (now claim 61).

13.  $-R^9$ ,  $-R^9R^{10}$  and  $-COR^9$  are amended to read  $-SR^9$ ,  $-NR^9R^{10}$  and  $-OCOR^9$ , respectively. These amended groups are disclosed in original Claim 8 and page 12, line 13.

14. The third structure in Claim 36 (now claim 62) is amended to delete three bonds from  $G_3$ ,  $G_4$  and  $G_5$ . The amended structure is disclosed in Claim 4 and page 10, last line.

15. The Examiner stated that the amendment to the additional active ingredient bisphosphonate compound is not described in the specification for any other bisphosphonate compounds other than alendronate. This is not so as sufficient examples are given at page 30, lines 23-25. New matter is not contained in Claim 49 (now claim 61).

16. Claim 50 (now claim 75) is amended to specifically define the “growth factor” intended as in previous Claim 51 which is canceled.

17a. Claim 37 (now claim 63) is amended to depend from Claim 33 (now claim 61). All the compounds referred to in Claim 37 (now claim 63) are encompassed by Claim 33 (now claim 61).

17b. “10h” in Claim 37 (now claim 63) is amended to --- 10H ---.

17c. “ $-R^9$ “ and “ $-R^9R^{10}$ “ in Claim 33 (now claim 61) are amended to ---  $-SR^9$  --- and ---  $-NR^9R^{10}$  ---, respectively. There is antecedent basis for the limitation in Claim 40 (now claim 65).

17d. “ $COR^9$ ” in Claim 33 (now claim 61) is amended to ---  $OCOR^9$  ---. There is antecedent basis for the limitation in Claim 41 (now claim 66).

17e. Claim 33 (now claim 61) states “ $R^5$  and  $R^6$ , or  $R^7$  and  $R^8$  are bonded, respectively, to form carbonyl, thiocarbonyl or imino”. The limitation “ $=NH$ ” in the definition of D in Claim 41 is encompassed by “imino” in Claim 34 (now claim 62).

17f. Claim 33 (now claim 61) states “ $R^2$  and  $R^3$  are independently hydrogen, alkyl, arylalkyl which may be substituted on its aromatic ring, or arylalkoxyalkyl which may be substituted on its aromatic ring, acyl, amidino, alkoxy carbonyl”. The limitation “ $C(=NH)NH_2$ ” is encompassed by “amidino” in Claim 33 (now claim 61).

17g-j. Claim 33 (now claim 61) states “ $R^5$ ,  $R^6$ ,  $R^7$  and  $R^8$  can be taken together with  $R^1$  or  $R^2$  and the bridging group which links  $R^5$ ,  $R^6$ ,  $R^7$  or  $R^8$  to  $R^1$  or  $R^2$  to form a carbocycle or heterocycle”. The limitations “2-aminopyrrol-1-yl”, “4-aminopiperid-1-yl”, “3-amino-4-hydroxypyrrrol-1-yl” and “3-amino-5-ethoxycarbonylpyrrol-1-yl” are encompassed by “heterocycle” in Claim 33 (now claim 61).

17k. Claim 41 (now claim 66) is amended to end with a period.

17l. "11H-i" in Claim 42 (now claim 67) is amended to read --- 11-di ---.

17m. "buthanamide" in Claim 42 (now claim 67) is changed to --- butanamide ---.

17n. "Aminoethyl" in Claim 42 is changed to --- Amino-ethyl".

17o. "hydroxylcarbamoyl" in the 7<sup>th</sup>, 8<sup>th</sup> and 9<sup>th</sup> species on page 19 of the response to the first action is amended to read --- hydroxypropylcarbamoyl ---. Support for the amendment can be found in Example Nos.254, 268 and 260 on pages 71 and 72 of the original specification.

17p. The meaning of "leaving group" is fully recognized by person skilled in the art. See the attached excerpt from Morrison & Boyd, "Organic Chemistry" 172-177, which fully explains the meaning of "leaving group".

17q and y. The limitation "2-hydroxypropyl" in the first moiety of the third row on page 22 is encompassed by "hydroxylalkyl" in Claim 33 (now claim 61).

17r-x, the rejections are overcome for the same reasons as Paragraphs 17d-j, respectively.

Counsel has made every effort to resolve the numerous issues relating to claim clarity, appropriate disclosure and antecedent basis. The examiner's cooperation is requested and counsel invites telephone discussions with the examiner to resolve any issues that may remain.

Reconsideration and allowance are solicited.

Respectfully submitted,

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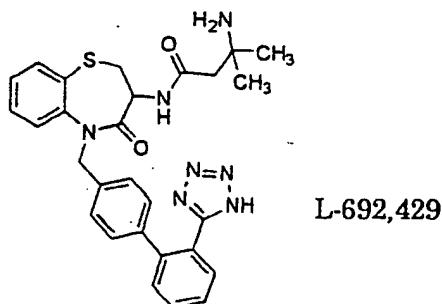
secretagogues, should be orally bioavailable, induce production or release of growth hormone, and act as synergistically with growth hormone releasing hormone.

Representative growth hormone secretagogues are disclosed in USP 3,239,345;

USP 4,036,979; USP 4,411,890; USP 5,206,235; USP 5,248,841; USP 5,310,017;

5 USP 5,310,737; USP 5,434,261; USP 5,552,385; USP 5,559,128; EP 144,230; EP 513,974; WO 94/07486; WO 94/08583; WO 94/11012; WO 94/13696; WO 95/03290; WO 95/09633; WO 95/12598; WO 95/13069; WO 95/14666; WO 95/16692; WO 95/16675; WO 95/17422; WO 95/17423; WO 95/34311; WO 96/02530; WO 96/05195; WO 96/13265; WO 96/15148; WO 96/22997; WO 96/24587; WO 96/35713; WO 96/38471; WO 97/00894; WO 96/24580; WO 97/06803; WO 97/07117; WO 97/11697; WO 97/15191; WO 97/22620; WO 97/23508; WO 97/24369 and Science, 260, 1640-1643 (1993), ~~the entire of all of which are herein incorporated by reference~~.

15 USP 5,206,235 issued April 27, 1993, describes a series of benzolactam compounds typified by the following structure. These compounds have demonstrated



clinical activity in humans in raising the growth hormone secretory levels (B.J. Gertz., Journal of Clinical Endocrinology and Metabolism, 77, 1393-1397 (1993)).

Second generation of growth hormone secretagogues is described in WO 94/13696, WO 96/15148. These compounds are typified by the following structure.

